Spinraza (nusinersen)

Policy Number: 5.02.540
Orignation: 03/2017
Last Review: 04/2018
Next Review: 04/2019

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Spinraza when it is determined to be medically necessary because the following criteria have been met.

When Policy Topic is covered

Initial Therapy – 4 doses (20ml); 3 months

Nusinersen is considered medically necessary for the patient who must have the following:

A. Spinal Muscular Atrophy (SMA) AND ALL of the following:
   1. Diagnosis was confirmed by genetic testing
   2. Type I, II, or III SMA
   3. Treatment is prescribed by or in consultation with a board certified neurologist
   4. Prescriber agrees to do a platelet count and coagulation test before each dose
   5. Patient must have a platelet count of ≥ 50,000 cells per microliter
   6. Prescriber agrees to do quantitative spot urine testing before each dose
   7. Obtain a baseline motor milestone score from ONE of the following assessments:
      a. HINE
      b. CHOP-INTEND
      c. Upper Limb Module (ULM)
      d. Hammersmith Functional Motor Scale (HFMS)

Continuation Therapy-3 doses (10ml); 12 months

Continuation of treatment with nusinersen beyond 3 months after initiation of therapy, and every 12 months thereafter, is considered medically necessary for the treatment of spinal muscular atrophy when patients have the following:

A. Spinal Muscular Atrophy (SMA) with ONE of the following:
   1. Type I SMA
      a. Improvement in motor milestone score from baseline
   2. Type II or III SMA:
a. Improvement in motor milestone score of 2 points from baseline

AND ALL of the following:

a. Treatment is prescribed by or in consultation with a board certified neurologist
b. Prescriber agrees to do a platelet count and coagulation test before each dose
c. Patient must have a platelet count of > 50,000 cells per microliter
d. Prescriber agrees to do quantitative spot urine testing before each dose

Injection: 12 mg/5 mL (2.4 mg/mL) in a single-dose vial; intrathecal

FDA-approved

- The recommended dosage is 12 mg (5 mL) per administration
- Initiate treatment with 4 loading doses; the first three loading doses should be administered at 14-day intervals; the 4th loading dose should be administered 30 days after the 3rd dose; a maintenance dose should be administered once every 4 months thereafter

When Policy Topic is not covered

Use of nusinersen is considered investigational when the criteria above are not met and for all other indications, including but not limited to non-5q-spinal muscular atrophy disorders, as well as Type 0 and Type 4 SMA.

Considerations

Spinraza requires prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service

Spinraza is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

Spinraza has a high risk of thrombocytopenia and coagulation abnormalities. Physicians should obtain a platelet count and appropriate coagulation laboratory testing at baseline and before each dose. No patient had a platelet count less than 50,000 cells per microliter in these studies. Additionally, due to the risk of renal toxicity, quantitative spot urine testing are required at baseline and before each dose.

In the clinical studies done for Spinraza the patients in these studies had or were likely to develop Type I, II, or III SMA. The clinical studies did not include Type 0 and IV.

Multiple tools have been developed in order to determine a baseline motor milestone score for patients with SMA. These assessments can also be utilized to measure improvement, and include: Hammersmith Infant Neurologic Exam (HINE), Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Upper Limb Module (ULM) and the Hammersmith Functional Motor Scale (HFMS).

The safety and effectiveness of Spinraza in pediatric patients from newborn to 17 years have been established.
Spinal Muscular Atrophy (SMA)

SMA is largely an inherited autosomal recessive disease caused by mutations in chromosome 5q that lead to a deficiency in SMN1-related proteins. In rare instances (2-3% of SMA), SMA can occur de novo, where a mutation occurs in an individual during egg or sperm production, rather than inheriting a defective copy of the gene from each parent. This deficiency results in degeneration of motor neurons causing muscle atrophy, particularly in the limbs and the muscles that control the mouth, throat and respiration. There are four types of SMA, types I, II, III, and IV which are defined based on the severity of muscle weakness and the age of symptom onset. SMA type I (Werdnig-Hoffmann disease) is the most severe. SMA type I-affected infants represent approximately 60% of SMA diagnoses and present with the disease by 6 months of age. These infants are profoundly hypotonic and often succumb to complications of the disease by their second year of life. SMA type II affected children (intermediate form) present with symptoms prior to 18 months of age and develop the ability to sit unaided but not the ability to stand or walk. Individuals affected by SMA type III (Kugelberg-Welander disease) are also generally diagnosed by 18 months but are able to stand and walk. SMA type III affected individuals may live into their thirties and beyond. SMA IV, the least severe, typically presents in the second or third decade of life, but is otherwise similar to type III.

SMN2, a closely related gene to SMN1 that also produces functional SMN, can compensate for SMN1 deficiency and modify the SMA phenotype. Therefore, although the role of SMN protein in motor neurons is not completely understood and the amount for normal functioning undefined, the phenotype of spinal muscular atrophy (type I, II, III, or IV) is largely related to the number of SMN2 gene copies present. The number of copies of SMN2 in individuals diagnosed with SMA has been found to negatively correlate with disease severity. For instance, infants diagnosed with SMA type I, are likely to have two copies or less of SMN2 and individuals with SMA type III and IV are likely to have three copies or more (Mailman, 2002).

A number of other motor neuron diseases exist, also termed SMA, that are caused by mutations in genes other than the SMN1 gene. These are referred to as non-5q- SMA diseases, meaning that the genes causing these forms of SMA are not located in the SMN region of chromosome 5.

The incidence of SMA is approximately 1 in 10,000 live births with an estimated carrier frequency of 1 in 50. Standard of care for SMA has historically been based on supportive therapy which includes nutrition, physical therapy, and respiratory assistance. SMA is the leading genetic cause of death in infants, but can affect individuals at any stage of life.

Nusinersen is an antisense oligonucleotide designed to treat SMA by altering SMN2 promoting increased production of functional SMN. Nusinersen is the first drug to receive FDA approval for the treatment of children and adults with SMA.

SMA is classified into 4 main categories (with additional subcategories) based on the age at the onset of symptoms and various motor milestones. Generally, early onset of disease directly correlates to severity of symptoms and rate of disease progression. There is no exact marker to classify these categories, and they are not well-distinguished by ICD-10-CM code.

- **Type 0**: The most severe form of SMA, symptoms can often be seen in the later stages of pregnancy. Fetal movements are less than expected and, after birth, the infant will have little ability to move and may not be able to breathe and swallow independently. Death occurs before the age of 6 months.
- **Type I (also called infantile SMA or Werdnig-Hoffman disease and subcategorized as IA, IB and IC)**: Onset within 6 months of birth and symptoms progress rapidly, and most infants die before 1 year of age from respiratory failure. About 60% of patients with SMA constitute of this phenotype.
- **Type II (also called intermediate SMA or Dubowitz disease)**: Onset within 6 to 18 months with a less severe progression. Typically, a child can sit independently if positioned, but is unable to walk. Many patients will ultimately lose the ability to sit independently. More than 70% of patients live beyond 25 years of age with adequate supportive care.
- **Type III (also called Kugelberg-Welander disease and subcategorized as IIIA and IIIB)**:
Onset after 18 months of age. Patients achieve the ability to walk but many will lose this ability later in the course of the disease. Lifespan is not affected, with wide-ranging reduction in muscle strength with a chronic course. The outcome depends primarily on the severity of muscle weakness at presentation rather than age of onset, but earlier onset tends to correlate with greater weakness.

- Type IV (also called adult-onset SMA): Usually presents in the third decade of life. Patients remain ambulatory but may have hip and shoulder girdle weakness mimicking a mild limb-girdle muscular dystrophy.

### SMA Classification:

<table>
<thead>
<tr>
<th>Type</th>
<th>Age of onset</th>
<th>Highest Function</th>
<th>Natural Age of Death</th>
<th>Copies of SMN2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Prenatal)</td>
<td>Prenatal</td>
<td>Respiratory failure</td>
<td>&lt; 1 month</td>
<td>1</td>
</tr>
<tr>
<td>I (Werdnig-Hoffman disease)</td>
<td>0-6 months</td>
<td>Never sit</td>
<td>&lt; 2 years</td>
<td>2</td>
</tr>
<tr>
<td>II (Dubowitz disease)</td>
<td>&lt; 18 months</td>
<td>Never stand</td>
<td>&gt; 2 years</td>
<td>3, 4</td>
</tr>
<tr>
<td>III (Kugelberg-Welander disease)</td>
<td>18 months-21 years</td>
<td>Stand or ambulatory</td>
<td>Adult</td>
<td>3, 4</td>
</tr>
<tr>
<td>IV (adult onset)</td>
<td>&gt; 21 years</td>
<td>Ambulatory</td>
<td>Adult</td>
<td>4-8</td>
</tr>
</tbody>
</table>

### Adverse Events and Warnings

Warnings and recommendations from the FDA PI Label (2016) include:

- **Thrombocytopenia and Coagulation Abnormalities:** Increased risk for bleeding complications; platelet count and coagulation laboratory testing required at baseline and before each dose of nusinersen.

- **Renal Toxicity:** Quantitative spot urine protein testing required at baseline and prior to each dose of nusinersen.

- The most common adverse reactions to nusinersen were lower respiratory infection, upper respiratory infection, and constipation.

### Rationale

On December 23, 2016 nusinersen was granted accelerated approval by the U.S. Food and Drug Administration (FDA) for the treatment of SMA. The FDA granted nusinersen fast-track, priority review and orphan drug designation (Product Information [PI] Label, 2016). Nusinersen is the first drug approved to treat children and adults with SMA, a rare and often fatal genetic disease affecting muscle strength and movement. Nusinersen is an antisense oligonucleotide, a drug class that does not cross the blood-brain barrier and as a result, it must be administered by intrathecal injection.

Nusinersen's approval was based on positive interim results of an unpublished Phase III, double-blind, controlled clinical trial, known as ENDEAR, conducted in infants, aged 7 months or younger at study entry, who were diagnosed with symptomatic infantile-onset SMA (Type I). Inclusion criteria specified confirmatory diagnosis of SMA consistent with type I severity had been determined by identification of two copies of SMN2 (see Background/Overview for more information), age of onset (symptom onset before 6 months of age), and symptom severity. A total of 82, out of 121 infants enrolled in ENDEAR
were included in the interim analysis. Study participants were enrolled 2:1 and all infants included in the interim analysis had died, withdrawn or completed at least 183 days (6 months) of treatment. Baseline disease characteristics were similar between study arms with the exception of the nusinersen-treatment group having a higher percentage of paradoxical breathing, pneumonia, respiratory symptoms, swelling/feeding difficulty and need for respiratory support. Also, 88% of the treatment group and only 77% of the control group, experienced symptoms within the first 3 months of life. Demographics were well balanced with the exception of the treatment group being an average of 31 days younger than the control group at the start of treatment (median age 175 vs. 206 days, respectively). Despite the treatment group having more severe symptoms at baseline, the trial found 40% of those treated, compared with 0% of those in the control arm, demonstrated improvement in motor milestones such as head control, sitting, crawling and standing (p<0.0001). Furthermore, as assessed by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), 63% (n=33) of infants treated with nusinersen improved by at least 4 points, whereas only 3% (n=1) achieved this improvement in the control arm. Similarly, 40% (n=12) of the control arm worsened by at least 4 points on the CHOP-INTEND test whereas only 4% (n=2) of the treatment arms experienced this decline in motor function. The most common adverse events that occurred in the treatment arm more often than the control arm were respiratory infections and constipation. Atelectasis, a serious adverse reaction, was more frequent in the treatment arm (14%) compared to the control arm (5%) (FDA PI Label, 2016). This clinical trial is now open-label and is ongoing.

Finkel and colleagues (2016) published nusinersen safety and efficacy data from a phase II open-label, dose-escalation study which enrolled 20 infants who were between 3 weeks and 7 months of age and had SMN1 homozygous gene deletion or mutation with onset of SMA symptoms between 3 weeks and 6 months of age (SMA type I); 17/20 participants had two copies of SMN2. Outcomes included several measures of safety as well as event free survival, change in the motor milestones portion of the Hammersmith Infant Neurological Exam-Part 2 (HINE-2) and the CHOP-INTEND motor function test. Time to death or permanent ventilation was compared with natural history data of infants with SMA (Finkel, 2014). At the time of the interim analysis the publication was based on, the 6-12 mg group (n=4; 6 mg loading doses administered on days 1, 15 and 85 and 12 mg doses on day 253 and every 4 months thereafter) had been followed for 9-32 months and received four to nine doses of nusinersen, whereas the 12 mg group (n=16; 12 mg doses administered on the same schedule as the 6-12 mg group) had been followed for 2-27 months and received two to eight doses. Although all study participants experienced adverse events, none were determined to have likely been related to nusinersen administration. The most common adverse events were respiratory-related which are frequent in infants with SMA. In the 12 mg dose group, incremental achievements of motor milestones (p<0.0001) and improvements in CHOP-INTEND motor function scores (p=0.0013) from baseline were reported. The median age at death or permanent ventilation was not reached and the Kaplan-Meier survival curve diverged significantly from a published natural history case series (p=0.0014). The results of this trial informed the design of the Phase III clinical study on which nusinersen’s approval was based.

A Phase I nusinersen dose-finding study (1, 3, 6 and 9 mg) in SMA types II and III enrolled 28 children aged 2-14 years (Chiriboga, 2016); 25/28 participants had 3 copies of SMN2. There were no safety or tolerability issues identified in this older cohort of children with SMA types II and III and a significant increase in the exploratory endpoint of Hammersmith Functional Motor Scale Expanded (HFMSE) scores was seen at the 9-mg dose (+3.1 points; p=0.016). Authors concluded that the risk-benefit profile was favorable for further investigation of nusinersen’s safety and efficacy in this population.

Package labeling noted that unpublished data from additional open-label, non-controlled trials support the safety and efficacy of nusinersen in both pre-symptomatic and symptomatic SMA disease presentation. The open-label clinical studies included symptomatic SMA study participants aged 30 days to 15 years old at the time of enrollment and pre-symptomatic participants ranging in age from 8 days to 42 days at enrollment. Nusinersen was determined to illicit an immunogenic response in 126 of the 173 individuals exposed to the drug in clinical trials who had baseline plasma samples evaluated for anti-drug antibodies (ADAs). At this time, the FDA has stated, "There are insufficient data to evaluate
an effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen” (FDA PI Label, 2016).

To date, there is no evaluable published data on the safety and efficacy of nusinersen in individuals with more than two copies of SMN2 or symptom onset after 6 months of age. There are four additional ongoing clinical trials evaluating nusinersen’s safety and efficacy in SMA, they include the following: (1) a Phase III study of type III SMA (late-onset) know as CHERISH (NCT 02292537; ClinicalTrials.gov; expected completion: June 2017 ), (2) a phase II randomized, double-blind, sham-procedure controlled study known as EMBRACE (NCT 02462759) for children diagnosed with SMA consistent with type II (intermediate disease severity) who were not eligible for enrollment in either ENDEAR or CHERISH, (3) an Expanded Access Program trial in infantile-onset SMA(NCT 02865109), and (4) an open-label follow-up study of those enrolled in completed trials of nusinersen, known as SHINE (NCT 02594124; clinicaltrials.gov).

References

Peer Reviewed Publications:


Government Agency, Medical Society, and Other Authoritative Publications:


5. Biogen Inc. Expanded Access Program (EAP) for nusinersen in participants with infantile-onset (consistent with type 1) spinal muscular atrophy (SMA). NLM Identifier: NCT02865109.


Websites for Additional Information


Billing Coding/Physician Documentation Information

Spinraza is considered a medical benefit.

<table>
<thead>
<tr>
<th>HCPCS</th>
<th>Description</th>
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<tr>
<td>J3490</td>
<td>Unclassified drugs [when specified as nusinersen (Spinraza)]</td>
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<tr>
<td>C9489</td>
<td><strong>Spinraza</strong> 12 MG/5ML SOLN C9489 Injection, nusinersen, 0.1 mg - see also J3490</td>
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<tr>
<td>J2326</td>
<td><strong>Spinraza</strong> 12 MG/5ML SOLN J2326 Injection, nusinersen, 0.1 mg (Code becomes effective for Medicare billing 1/1/18)</td>
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<tr>
<th>CPT</th>
<th>Description</th>
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<tr>
<td>81401</td>
<td>Code used for testing Description = Molecular Pathology Procedure Level 2</td>
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<td>81329</td>
<td>SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed</td>
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<td>81336</td>
<td>SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence</td>
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<td>96450</td>
<td>Chemotherapy administration, into CNS, requiring and including spinal puncture</td>
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<tr>
<th>ICD-10 Diagnosis</th>
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<tr>
<td>G12.0</td>
<td>Infantile spinal muscular atrophy, type I (Werdnig-Hoffman)</td>
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<td>G12.1</td>
<td>Other inherited spinal muscular atrophy [includes types II,III (Kugelberg-Welander) and IV]</td>
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<td>G12.8</td>
<td>Other spinal muscular atrophies and related syndromes</td>
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<td>G12.9</td>
<td>Spinal muscular atrophy, unspecified</td>
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Additional Policy Key Words

N/A

Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Update</th>
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<tbody>
<tr>
<td>03/2017</td>
<td>New policy titled Spinraza (nusinersen)</td>
</tr>
<tr>
<td>12/2017</td>
<td>Added C9489 and J2326</td>
</tr>
<tr>
<td>01/2018</td>
<td>Changed renewal period to 12 months</td>
</tr>
<tr>
<td>03/2018</td>
<td>Reviewed – no changes made</td>
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<tr>
<td>12/2018</td>
<td>Added new CPT codes for SMN1 genetic testing</td>
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